Engineering Smarter and Stronger T Cells for Cancer Immunotherapy

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Adoptive T cell therapy for cancer has demonstrated exciting potential in treating relapsing cancers. In particular, T cells that express synthetic chimeric antigen receptors (CARs) specific for the B-cell marker CD19 have shown impressive results in clinical trials for various B-cell malignancies, prompting avid interest from both scientific and entrepreneurial communities in recent years. However, CD19 CAR-T cell therapy remains the only robustly effective T-cell immunotherapy to date, and several obstacles remain to be overcome before the full potential of adoptive T-cell therapy can be realized. My laboratory is pursuing several strategies for the engineering of T cells with stronger anti-tumor functions and greater robustness against evasive mechanisms employed by cancer cells. I will discuss the design, construction, and implementation of multi-input CARs to increase tumor specificity and decrease the probability of mutational escape by tumor cells. I will present the design of synthetic circuits to reroute signaling pathways triggered by tumor-secreted cytokines, thus negating the immunosuppressive effects of the tumor microenvironment. Finally, I will discuss efforts to engineer a cytotoxic protein that triggers target-cell death upon recognition of intracellular oncoproteins, thus expanding the repertoire of detectable tumor markers beyond surface-bound antigens. These strategies combine to address critical limitations facing adoptive T-cell therapy, providing potential treatment options for diseases that are otherwise incurable with current technology.